MAIL STOP AF

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Patent Application Of: Rozlyn A. Krajcik, *et al.*			
Conf. No.:	5919	Group Art Unit:	1617
Appln. No.:	10/073,607	Examiner:	Jennifer M. Kim
Filing Date:	February 11, 2002	Attorney Docket No.:	4555-43U1
Title:	METHODS AND COMPOSITIONS FOR THE TREATMENT OF ALOPECIA AND OTHER DISORDERS OF THE PILOSEBACEOUS APPARATUS		

DECLARATION UNDER 37 C.F.R. § 1.132 OF ROZLYN A. KRAJCIK, PH.D., R.PH.

I, Rozlyn A. Krajcik, Ph.D., R. Ph., hereby delare as follows:

1. I am the same Rozlyn A. Krajcik named as a coinventor and co-applicant in the above-identified application. As such, I know the invention and have read the application, the Office Action of December 28, 2004, and the prior art cited in that Office Action, as well as the claims pending in the accompanying Amendment.

2. I graduated summa cum laude from the University of Pittsburgh School of Pharmacy in 1973 and for the following 13 years managed large retail pharmacies and gained hospital experience. I earned a doctoral degree from Wright State University in its multidisciplinary Biomedical Sciences Program in 1992 and have since been employed by the Orentreich Foundation for the Advancement of Science, Inc. (OFAS), the assignee of the present invention and application. My primary research focus has been the impact of endocrinological disorders on skin health and hair growth. Other research interests include biomaterials applications, aging

interventions, and serum biomarkers for common diseases, e.g., prostate and breast cancers, dementia, and autoimmune illnesses. My curriculum vitae is attached as Exhibit A.

3. As Assistant Director – Scientific Affairs and Director of Laboratories at OFAS for 12 years, I have been extremely involved personally and in working with others involving research relating to alopecia and other disorders of the pilosebaceous apparatus. Based on this experience, my prior experience as mentioned in paragraph 1 above and in my curriculum vitae attached as Exhibit A, including my experience as a Registered Pharmacist, and my education leading to my Ph.D. degree in Biomedical Sciences, I consider myself and am considered by others to be a person who is an expert in the art relating to the subject matter of this application. I also am familiar with and have worked with those who are persons of ordinary skill in the art relating to the subject matter of this application, who are generally people with advanced degrees in life sciences, and several years of experience. As a result, I am familiar with the capabilities of those of ordinary skill in this art.

4. In view of the statements in the outstanding Office Action, I researched the structures and functions of chlorhexidine and certain biguanide compounds, including metformin, a preferred biguanide compound that is a recognized insulin sensitivity increasing substance (ISIS) that was used in the Examples of the application.

5. The focus of the application is on the use of an ISIS, which is specifically claimed in claim 31, the only non-withdrawn pending independent claim, to treat mammalian alopecia. The invention is based on the discovery, after considerable research, of the new use of insulin sensitivity increasing substances to treat alopecia and other disorders of the pilosebaceous apparatus. As a result, the function of a substance as an ISIS is integral to the claimed invention. Prior to the present invention, no one knew, based on the lack of any publications, that an ISIS would, or even could, effectively treat alopecia or other disorders of the pilosebaceous apparatus. The mere possibility, so far unrecognized prior to the present application, that a substance might, in retrospect, be an ISIS, is not an appropriate determination that such substance really is an ISIS.

6. The primary reference relied upon in the Office Action is an abstract from the June 6, 1988 issue of Drug Launches ("Drug Launches"), relating to a product called Novian Forte made

by a Korean company, disclosing the uses: "Stimulation of hair growth, prevention of hair loss." The reference identifies the following active ingredients of Novian Forte in the indicated percentages, without indicating the purpose or function of any of them: reisogen, 3%; chlorhexidine gluconate, 0.5%; swertiol, 0.2%; glycyrrhizink, 0.12%; capsicum tinc, 3%; nicotinamide, 0.25%; vitamin B6, 0.02%; and 1-menthol, 0.05%. The Office Action indicates that the reference "teaches chlorhexidine (biguanide compound) is commercially available available in a liquid formulation of 150ml for the stimulation of hair growth and prevention of hair loss," and therefore concludes that the present invention of treating alopecia would have been obvious due to the use of the chlorhexidine-containing formulation. I strongly disagree with either the implication of the conclusion that clorhexidine provides any function relating to stimulation of hair growth or prevention of hair loss, or with the implication of the conclusion that requires a determination that chlorhexidine is an ISIS.

7. Attached as Exhibit B is a copy page 361 of the 13th Edition of *The Merck Index* (2001) (hereinafter "*Merck*"), with respect to monograph number 2108 relating to chlorhexidine. Based on the description in the monograph and chemical formula, chlorhexidine is a bisbiguanide. The monograph identifies chlorhexidine as a "bisbiguanide with bacteriostatic activity." It further characterizes both the human and veterinary therapeutic categories as "antiseptic; disinfectant." Chlorhexidine's antiseptic or disinfectant antimicrobial function is dependent upon the chlorinated phenyl rings. A significant structural difference between chlorhexidine and metformin, the exemplary biguanide compound mentioned throughout the application, including the examples, is readily apparent from monograph number 5963 at page 1061 of *Merck*, attached as Exhibit C. *Merck* characterizes the therapeutic category of metformin as an antidiabetic agent, which is a therapeutic use of an ISIS, though not all antidiabetic agents are insulin sensitivity increasing substances.

8. Attached as Exhibit D is a printout from Thomson MICROMEDEX (http://eresources.library.mssn.edu), relating to its entry for chlorhexidine. As noted at page 1 of Exhibit D, chlorhexidine is considered an antibacterial (dental) product. Among the indications listed at pages 1-2 of Exhibit D, are various treatments for gingivitis, mouth infections, stomatitis and dental plaque. Notably absent is any mention or suggestion that chlorhexidine would be considered an ISIS. It is important to note that chlorhexidine is not readily absorbed from the

gastrointestinal tract (Exhibit D, page 3), nor would chlorhexidine penetrate the skin. These characteristics distinguish chlorhexidine significantly from metformin and other such small-molecule biguanides, since they, like metformin, are readily absorbed from the gastrointestinal tract and penetrate the skin for delivery to the pilosebaceous apparatus as claimed in claim 31 of this application. Chlorhexidine would not be so usable.

9. A literature review failed to locate any evidence that chlorhexidine is an ISIS. In fact, the literature suggests that if chlorhexidine were to be delivered to the cells comprising hair follicles, it would interfere with glycolysis, a metabolic activity stimulated by insulin and required for energy production in hair follicles. Lactic acid production (a product of glycolysis) was shown to decrease after treatment of dental plaque with chlorhexidine. *See*, E. Giersten, et al., *J Dent Res.*, 68 (6):1132-1134 (June, 1989), a copy of the abstract of which is attached as Exhibit E. The interference occurs primarily by damaging cellular membranes causing leakage of metabolites from cells. Thus, the mechanism of action of chlorhexidine's inhibition of glycolysis in the bacteria associated with plaque is through membrane disruption, as reported in Y. Iwami, et al. *Oral Microbiol Immunol.*, 10 (6):360-364 (December, 1995), the abstract of which is attached as Exhibit F. The Iwami, et al. authors note that there were no direct effects on enzymes involved in glycolysis (either decreased or increased activity). This suggests that even this one aspect of many involved in insulin activity, namely stimulation of glycolysis, is not a function or characteristic of chlorhexidine. While the membrane damaging effect noted in the Iwami, et al. reference relates to bacterial cells, such damaging effect would also be expected to extend to mammalian cell types.

10. Additional supporting evidence shows that chlorhexidine interferes with sugar transport and metabolism. *See,* C.W. Keevil, et al., *Arch Oral Biol.* 29 (11): 871-878 (1984), the abstract of which is attached as Exhibit G; J.S. van der Hoeven. et al., *Carries Res.*, 27 (4): 298-302 (1993), the abstract of which is attached as Exhibit H; and E. Giersten, et al. *Carries Res.*, 29(3): 181-187 (1995), the abstract of which is attached as Exhibit I. As with Iwami, et al., although the mechanism in these papers is directed to bacteria, it can be expected to extend also to mammalian cell types.

11. The evidence summarized above and present in the attached Exhibits makes it clear that chlorhexidine is not an ISIS and that not all biguanide compounds would be ISISes.

12. Although Drug Launches asserts that the composition stimulates hair growth and prevents hair loss, there is no indication whatsoever in its meager disclosure that the Novian Forte product is an ISIS or that any of its ingredients would be considered an ISIS.

13. Based on the evidence set forth above and referenced in Exhibits B-I, it is my opinion that a person of ordinary skill in this art would not consider it obvious to treat alopecia with an ISIS as claimed in this application in view of Drug Launches, even assuming only for the sake of argument that Novian Forte actually is commercially available.

I hereby declare that all statements made herein of my own knowledge are true and that all statements on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the patent application or any patent issuing thereon.

Date: 9-28-05

Rozlyn A. Krajcik

Rozlyn A. Krajcik, Ph.D., R.Ph.

CURRICULUM VITAE

Name	Rozlyn A. Krajcik, PhD, RPh	
Office	Orentreich Foundation for the Advancement of Science, Inc. 855 Route 301, Cold Spring, NY 10516	
Date of Birth	February 3, 1951	
Education	University of Pittsburgh, Pittsburgh, PA: BS Pharm Wright State University, Dayton, OH: PhD (Biomedical Sciences)	1973 1992
Licenses	Ohio State Pharmacists License (#03-3-10556)	
Professional Society Memberships	American Association of Hypertension American Association for the Advancement of Science Biomaterials Society New York Academy of Sciences	

Publications

1. Krajcik R, Orentreich DS, Orentreich N
   Plasmagel™: A novel injectable autologous material for soft tissue augmentation.
   Journal of Aesthetic Dermatology and Cosmetic Surgery 1(2):109-115, 1999.

2. Borofsky ND, Vogelman JH, Krajcik RA, Orentreich N
   Utility of insulin-like growth factor-1 as a biomarker in epidemiological studies.
   Clinical Chemistry 48(12):2248-2251, 2002.

3. Krajcik RA, Borofsky ND, Massardo S, Orentreich N
   Insulin-like growth factor-I (IGF-I), IGF-binding proteins, and breast cancer.
   Cancer Epidemiology, Biomarkers and Prevention 11(12):1566-73, 2002.

4. Zimmerman JA, Malloy V, Krajcik R, Orentreich N
   Nutritional control of aging. (Presented at the Neuroendocrinology of Aging Conference in Austria, August 2002.)
   Experimental Gerontology 38(1-2):47-52, 2003.

5. Krajcik RA, Vogelman JH, Malloy VL, Orentreich N
   Transplants from balding and hairy androgenetic alopecia scalp regrow hair comparably well on immunodeficient mice.
   Journal of the American Academy of Dermatology 48(5):752-59, 2003.

6. Krajcik RA, Massardo S, Orentreich N
   No association between serum levels of tumor necrosis factor-α (TNF-α) or the soluble receptors sTNFRI and sTNFR2 and breast cancer risk.
   Cancer Epidemiology, Biomarkers and Prevention 12(9):945-46, 2003.

7. Malloy VL, Krajcik RA, Bailey SJ, Hristopoulos G, Plummer JD, Orentreich N.
   Methionine restriction decreases visceral fat mass and preserves insulin action in aging male Fischer 344 Rats independent of energy restriction.
   Submitted to Aging Cell, July 2005.

Patent

1. Krajcik R, Orentreich N. Materials for soft tissue augmentation and methods of making and using same. US Patent Application #09/309,689. *Patent pending.*

Investigational Device Exemption

1. Application #G990034/S3 for the Clinical Investigation of Microdroplet Injection of Silskin™ 1000 Centistoke Silicone Oil for Soft Tissue Augmentation approved in 2001.

teladone; Supona. C_{12}-
I 3.92%, Cl 29.58%, O
ontains at least 90% of
rt *et al.*, **US 3003916**
, **US 3102842** (1963 to
. *Food Chem.* **14,** 352
in, D. E. Hopkins, *J.*
tson *et al., Biochem. J.*
I. Ambrose *et al., Tox-*
Bunyan *et al., Pestic.*

$bp_{0.5}$ 167-170°. Vapor
1.5272. Soly in water
ne, ethanol, propylene
rosive to metal. Toxic
66 orally (Ambrose).

N-(4-Chlorophenyl)-
diamide; 1-(*p*-chloro-
rophenyl-N^5-isopropyl-
$C_{11}H_{16}ClN_5$; mol wt
%, N 27.60%. Prepn:
urd *et al., ibid.* **1948,**
uf of acetate: Gailliot,
A. **51,** 7411e (1957).
macol. Exp. Ther. **90,**

29°.
als from acetone, mp

RP-3359; SN-12837;
20. Crystals from wa-
(alc): 259 nm. Sol in
sol in chloroform and
ally in rats: 200 mg/kg

2-Methyl-4-(2,2,2-tri-
ethyl-2-hydroxy-4-(2,
-hydroxy-2-methyl-4-
; Chloralodol; Lora
Cl_3O_3; mol wt 265.56.
%. Prepd from chloral
n, US 2931838 (1960

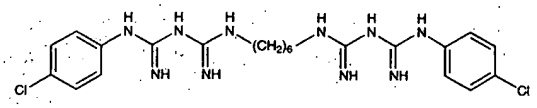
CCl_3

-104°. Readily sol in
r; slightly sol in CCl_4.

Note: This is a controlled substance (depressant): **21 CFR,** 1308.13.

THERAP CAT: Hypnotic.

2108. Chlorhexidine. [55-56-1] *N,N''*-Bis(4-chlorophenyl)-3,12-diimino-2,4,11,13-tetraazatetradecanediimidamide; 1,1'-hexamethylenebis[5-(*p*-chlorophenyl)biguanide]; 1,6-bis-[*N'*-(*p*-chlorophenyl)-N^5-biguanido]hexane; 1,6-bis(N^5-*p*-chlorophenyl-*N'*-diguanido)hexane; 1,6-di(4'-chlorophenyldiguanido)hexane; 10040. $C_{22}H_{30}Cl_2N_{10}$; mol wt 505.46. C 52.28%, H 5.98%, Cl 14.03%, N 27.71%. Bisbiguanide with bacteriostatic activity. Prepn: Rose, Swain, *J. Chem. Soc.* **1956,** 4422; *eidem,* **US 2684924** (1954 to I.C.I.). Antibacterial activity and acute toxicity: G. E. Davies *et al., Brit. J. Pharmacol.* **9,** 192 (1954). Review of toxicology and clinical uses: D. M. Foulkes, *J. Periodont. Res.* **8,** Suppl. 12, 55-60 (1973). Series of articles on clinical efficacy in gingivitis and plaque control: *ibid.* **21,** Suppl. 16, 1-89 (1986).



Crystals from methanol; mp 134°. Strong alkaline reaction. Soly in water at 20°: 0.08% (w/v).

Dihydrochloride. [3697-42-5] Lisium. $C_{22}H_{30}Cl_2N_{10}$·2HCl; mol wt 578.38. Crystals, dec 260-262°. Soly in water at 20°: 0.06 g/100 ml.

Diacetate. [56-95-1] Chlorasept 2000; Nolvasan. $C_{22}H_{30}Cl_2N_{10}$·$2C_2H_4O_2$; mol wt 625.56. Crystals, mp 154-155°. Neutral reaction. Soly in water at 20°: 1.9 g/100 ml. Aq solns dec when heated above 70°. Soluble in alcohol, glycerol, propylene glycol, polyethylene glycols. LD_{50} orally in mice: 2 g/kg (Davies).

D-Digluconate. [18472-51-0] Chlorhexamed; Bacticlens; Corsodyl; Gingisan; Hibiclens; Hibident; Hibidil; Hibiscrub; Hibital; Hibitane; Peridex; pHiso-Med; Plac Out; Rotersept; Secalan; Sterilon; Unisept. Soly in water at 20°: >50% (w/v). LD_{50} in mice (mg/kg): 22 i.v.; 1800 orally (Foulkes).

THERAP CAT: Antiseptic; disinfectant.

THERAP CAT (VET): Antiseptic; disinfectant.

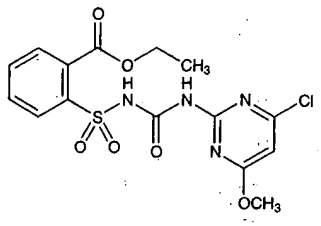
2109. Chloric Acid. [7790-93-4] $ClHO_3$; mol wt 84.46. Cl 41.98%, H 1.19%, O 56.83%. $HClO_3$. Prepd from barium chlorate and sulfuric acid: Lamb *et al., J. Am. Chem. Soc.* **42,** 1643 (1920); from sodium chlorate using ion-exchange resins: Klement, *Z. Anorg. Allgem. Chem.* **260,** 271 (1949).

Known in aq soln only. Aq solns are stable if pure and protected from light. 1% aq soln d_4^{18} 1.0044; 6% soln d_4^{18} 1.0344; 10% soln d_4^{18} 1.0594; 16% soln d_4^{18} 1.0991; 20% soln d_4^{18} 1.1273; 24% soln d_4^{18} 1.1568. A 40% soln corresponds to $HClO_3.7H_2O$, d_4^{20} 1.282. If higher concns are attempted by evaporation the soln begins to dec with evolution of chlorine and oxygen and formation of perchloric acid.

Caution: Strongly irritating to skin, mucous membranes.

USE: Oxidizing agent; with H_2SO_3 as catalyst in acrylonitrile polymerization.

2110. Chlorimuron-ethyl. [90982-32-4] 2-[[[[(4-Chloro-6-methoxy-2-pyrimidinyl)amino]carbonyl]amino]sulfonyl]-benzoic acid ethyl ester; ethyl 2-[[[[(4-chloro-6-methoxypyrimidin-2-yl)amino]carbonyl]amino]sulfonyl]benzoate; DPX-F6025; Classic. $C_{15}H_{15}ClN_4O_6S$; mol wt 414.83. C 43.43%, H 3.64%, Cl 8.55%, N 13.51%, O 23.14%, S 7.73%. Selective sulfonylurea herbicide. Prepn: A. D. Wolf, **AT 8316181**; *idem,* US **4547215** (1984, 1985 both to Du Pont). Effect on plant growth and pigment synthesis: R. M. Devlin, Z. K. Koszanski, *Proc. Ann. Meet. Northeast. Weed Sci. Soc.* **40,** 115 (1986). Metabolism by plants: H. M. Brown, S. M. Neighbors, *Pestic. Biochem. Physiol.* **29,** 112 (1987). Field trial in soybeans: G. N. Rhodes *et al., Tenn. Farm Home Sci.* **142,** 21 (1987). HPLC determn in crops: J. L. Prince, R. A. Guinivan, *J. Agr. Food Chem.* **36,** 63 (1988). Brief review: J. S. Claus, *Weed Technol.* **1,** 114-115 (1987).



Crystals from butyl chloride, mp 198-201°. Soly (ppm): acetone 71000, acetonitrile 31000, benzene 8000, methylene chloride 153000, water (pH 7) 1200, (pH 6.5) 450, (pH 5) 11. LD_{50} in male, female rats (mg/kg): 4102, 4236 orally (Claus).

USE: Herbicide.

2111. Chlorinated Lime. [7778-54-3] Bleaching powder. Improperly called ***"chloride of lime"*** or ***"calcium oxychloride"***. A relatively unstable chlorine carrier in solid form; a complex chemical compd of indefinite composition, presumably consisting of varying proportions of $Ca(OCl)_2$, $CaCl_2$, $Ca(OH)_2$ and H_2O in its molecular structure. Maximum available chlorine content approaches 39%. Commercial products usually range between 24% and 37% of available chlorine.

White or grayish-white powder; strong odor of chlorine. On exposure to air it becomes moist and rapidly decomposes. Most of it dissolves in water or alcohol. *Keep dry and tightly closed.*

Caution: Strong solns irritate skin. Inhalation of fumes may cause laryngeal and pulmonary irritation, pulmonary edema, death. Ingestion may produce severe oral, esophageal, gastric irritation.

USE: Bleaching of wood pulp, linen, cotton, straw, oils, soaps, and in laundering; oxidizer in calico printing to obtain white designs on a colored ground; destroying caterpillars; disinfecting drinking water, sewage, etc.; as a decontaminant for mustard gas and similar substances.

THERAP CAT: Disinfectant.

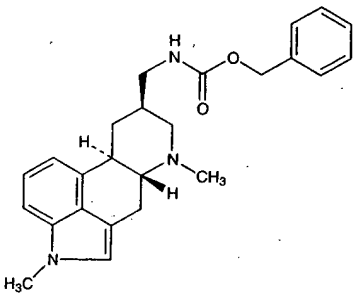
THERAP CAT (VET): Disinfectant for premises. Has been used as a topical antiseptic for superficial wounds.

2112. Chlorine. [7782-50-5] Cl; at. wt 35.4527; at. no. 17; valences 1, 3, 5, 7. A halogen; Group VIIA (17). Does not occur as elemental state, Cl_2, in nature. Abundance in igneous rock (95% of earth's crust): 0.031% by wt; in seawater: 1.9% by wt (primarily as NaCl). Naturally occurring stable isotopes (mass numbers): 35 (75.77%), 37 (24.23%); known artificial radioactive isotopes: 31-34, 36 (longest-lived known isotope, $T_{1/2}$ 3.0×10^5 yrs; β^-; EC decay), 38-46, 48. Discovered in 1774 by C. W. Scheele; recognized as an element in 1810 by H. Davy. Commercial sources: seawater, ocean derived mineral deposits, brines from lakes, wells and springs. Industrial prepn from brine in electrolytic cells. Lab prepn from MnO_2 and HCl: Schmeisser in *Handbook of Preparative Inorganic Chemistry* **vol. 1,** G. Brauer, Ed. (Academic Press, New York, 2nd ed., 1963) p 272. Cosmogenic production and determn of ^{36}Cl for geological dating: H. E. Gove, *Phil. Trans. Royal Soc. London, A* **323,** 103 (1987); M. G. Zreda *et al., Earth Planet. Sci. Letters* **105,** 94 (1991). *Reviews: Ciba Review* **vol. 12,** no. 139 (Aug. 1960); *Chlorine,* J. S. Sconce, Ed., A.C.S. Monograph Series, no. **154** (Reinhold, New York, 1962) 901 pp; *MTP Int. Rev. Sci.: Inorg. Chem., Ser. One,* **vol. 3,** V. Gutmann, Ed. (Butterworths, London, 1972); A. J. Downs, C. J. Adams, "Chlorine, Bromine, Iodine and Astatine" in *Comprehensive Inorganic Chemistry,* **vol. 2,** J. C. Bailar, Jr. *et al.,* Eds. (Pergamon Press, Oxford, 1973) pp 1107-1594; *Chemistry of the Elements,* N. N. Greenwood, A. Earnshaw, Eds. (Pergamon Press, New York, 1984) pp 920-1041; L. C. Curlin, T. V. Bommaraju in *Kirk-Othmer Encyclopedia of Chemical Technology* **vol. 1** (Wiley-Interscience, New York, 4th ed., 1994) pp 938-1025. Review of potential human health and environmental adverse effects of chlorine and its compounds: E. Delzell *et al., Reg. Toxicol. Pharmacol.* **2,** S1-S1056 (1994).

Greenish-yellow, diatomic gas; suffocating odor. mp −101.00°. bp −34.05°. d^{20} at 6.864 atm 1.4085 (liq); d^{-35} at 0.9949 atm 1.5649 (liq). d (relative to air) 2.48. Heat capacity

...ing this section.

amino)methyl]-1,6-dimethylergoline I benzyl ester; D-*N*-carboxydihydro-1-methyllysergamine I benzyl ester; D-[(4,6,6a,-7,8,9,10,10a-octahydro-4,7-dimethyl-10aα-indolo[4,3-*fg*]quinolin-9β-yl)methyl]carbamic acid benzyl ester; methergoline; Liserdol; Contralac. $C_{25}H_{29}N_3O_2$; mol wt 403.52. C 74.41%, H 7.24%, N 10.41%, O 7.93%. Serotonin 5HT-receptor antagonist. Prepn: Bernardi *et al., Gazz. Chim. Ital.* **94,** 936 (1964); Camerino *et al.,* **US 3238211** (1966 to Farmitalia). Pharmacology: C. Beretta *et al., Nature* **207,** 421 (1965). Metabolic studies: Arcamone *et al., Boll. Chim. Farm.* **110,** 704 (1971). Mode of action study: L. Krulich *et al., Endocrinology* **108,** 1115 (1981). Clinical antiprolactin activity: F. Scapin *et al., Eur. J. Clin. Pharmacol.* **22,** 181 (1982); A. Caballero *et al., J. Reprod. Med.* **32,** 115 (1987).

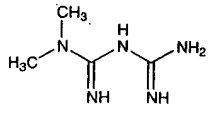


Crystals from benzene + ether, mp 146-149°. $[\alpha]_D^{28}$ −7 ±2°. uv max: 291 nm ($E_{1cm}^{1\%}$ 165). Very sol in pyridine; sol in alc, acetone, chloroform. Practically insol in benzene, ether, water. LD_{50} in mice (mg/kg): 85 i.p., 430 orally; in rats (mg/kg): >800 orally (Beretta).

THERAP CAT: Prolactin inhibitor.

THERAP CAT (VET): Prolactin inhibitor.

5963. Metformin. [657-24-9] *N,N*-Dimethylimidodicarbonimidic diamide; 1,1-dimethylbiguanide; *N,N*-dimethyldiguanide; *N'*-dimethylguanylguanidine; DMGG; LA-6023. $C_4H_{11}N_5$; mol wt 129.16. C 37.20%, H 8.58%, N 54.22%. Oral hypoglycemic agent. Prepn: Werner, Bell, *J. Chem. Soc.* **121,** 1790 (1922); Shapiro *et al., J. Am. Chem. Soc.* **81,** 3728 (1959). Use as antidiabetic: J. J. Sterne, **US 3174901** (1965 to Jan Marcel Didier Aron-Samuel). Toxicity: *Rx Bulletin* **3,** 25 (1972). Pharmacokinetics in man: G. T. Tucker *et al., Brit. J. Clin. Pharmacol.* **12,** 235 (1981). Review of pharmacology: L. S. Hermann, *Diabete Metab.* **5,** 233-245 (1979). Efficacy in NIDDM: R. A. DeFronzo *et al., N. Engl. J. Med.* **333,** 541 (1995). Metabolic effects and mechanism of action study: M. Stumvoll *et al., ibid.* 550.



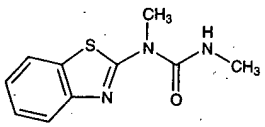
Hydrochloride. [1115-70-4] Diabetosan; Diabex; Glucophage; Metiguanide. $C_4H_{11}N_5.HCl$; mol wt 165.63. Prisms from water, mp 232° (Werner, Bell); crystals from propanol, mp 218-220° (uncorr) (Shapiro). Sol in water, 95% alcohol. Practically insol in ether, chloroform. LD_{50} in rats (mg/kg): 1000 orally, 300 s.c. (*Rx Bulletin*).

***p*-Chlorophenoxyacetate (salt).** [25672-33-7] Glucinan. $C_4H_{11}N_5.C_8H_7ClO_3$; mol wt 315.76.

Embonate. [34461-22-8] Metformin pamoate; Stagid. $(C_4H_{11}N_5)_2.C_{23}H_{16}O_6$; mol wt 646.70.

THERAP CAT: Antidiabetic.

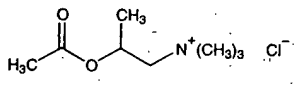
5964. Methabenzthiazuron. [18691-97-9] *N*-2-Benzothiazolyl-*N,N'*-dimethylurea; 1-(2-benzothiazolyl)-1,3-dimethylurea; metabenzthiazuron; MBU; Bayer 5633; Bayer 74283; Tribunil. $C_{10}H_{11}N_3OS$; mol wt 221.28. C 54.28%, H 5.01%, N 18.99%, O 7.23%, S 14.49%. Derivative of urea. Prepn and use as pre-emergence herbicide: N. E. Searle, **US 2756135** (1956 to du Pont). Use as pre- and post-emergence herbicide in wheat and barley: H. Hack *et al.,* **GB 1085430** (1967 to Bayer). Herbicidal properties: H. Hack, *Pflanzenschutz-Nachr.* **22,** 331 (1969). Toxicity studies: G. Kimmerle, E. Löser, *ibid.* 351. Use in winter cereals: D. C. Clark *et al., Proc. 12th Brit. Weed Control Conf.* 163 (1974). Mode of action: G. F. Collet, *Weed Res.* **9,** 340 (1969). Long-term effect on soil: P. L. Huge, *Pflanzenschutz-Nachr.* **34,** 97 (1981). Brief review: P. Lours, *Def. Veg.* **24,** 91 (1970).



White crystals from benzene, mp 119-120.5°. Soly in water at 20°: 59 ppm. Sol in organic solvents. Vapor pressure at 20°: $<10^{-6}$ mm Hg. LD_{50} in mice (mg/kg): >1000 orally; in male, female rats (mg/kg): >2500, >2500 orally; 540, 315 i.p. (Kimmerle, Löser).

USE: Selective herbicide.

5965. Methacholine Chloride. [62-51-1] 2-(Acetyloxy)-*N,N,N*-trimethyl-1-propanaminium chloride; acetyl-β-methylcholine chloride; *O*-acetyl-β-methylcholine chloride; (2-hydroxypropyl)trimethylammonium chloride acetate; (2-acetoxypropyl)trimethylammonium chloride; trimethyl-β-acetoxypropylammonium chloride; Amechol; Provocholine. $C_8H_{18}ClNO_2$; mol wt 195.69. C 49.10%, H 9.27%, Cl 18.12%, N 7.16%, O 16.35%. Parasympathomimetic bronchoconstrictor. Prepn: R. T. Major, J. K. Cline, **US 2040146** (1936 to Merck & Co.). Mechanism of ganglionic blockade in cats: R. L. Volle, *J. Pharmacol. Exp. Ther.* **158,** 66 (1967). Clinical diagnostic efficacy in bronchial asthma: S. L. Spector, R. S. Farr, *J. Allergy Clin. Immunol.* **56,** 308 (1975); J. G. Easton, I. Hirata, *Ann. Allergy* **50,** 171 (1983).



White, hygroscopic needles from ether, mp 172-173°. Slight odor of dead fish. Freely sol in water, alcohol, chloroform. Insol in ether. Aq solns are neutral to litmus. Should not be handled in very moist atmosphere. Bromide is less hygroscopic.

Antidote: Atropine.

THERAP CAT: Cholinergic. Diagnostic aid (bronchial asthma).

5966. Methacrifos. [62610-77-9] (2*E*)-3-[(Dimethoxyphosphinothioyl)oxy]-2-methyl-2-propenoic acid methyl ester; 3-hydroxy-2-methylacrylic acid methyl ester, *O*-ester with *O,O*-dimethyl phosphothioate; methyl (*E*)-3-(dimethoxyphosphinothioyloxy)-2-methylacrylate; CGA-20168; Damfin. $C_7H_{13}O_5PS$; mol wt 240.22. C 35.00%, H 5.45%, O 33.30%, P 12.89%, S 13.35%. Organophosphorus insecticide effective against arthropod pests in stored grains. Prepn: E. Beriger, L. Pinter, **ZA 67 04184**; *eidem,* **US 3594454** (1967, 1971 both to Ciba); *eidem,* **BE 766000**; *eidem,* **US 3923932** (1971, 1975 both to Ciba-Geigy). GLC determn of residues in stored grain: J. Desmarchelier *et al., Pestic. Sci.* **8,** 473 (1977). Efficacy and long-term stability: R. L. Kirkpatrick *et al., J. Econ. Entomol.* **75,** 277 (1982). Comparative field trial in stored sorghum: M. Bongston *et al., Pestic. Sci.* **14,** 385 (1983). Comprehensive description: R. Wyniger *et al., Proc. Brit. Crop Prot. Conf. - Pests Dis.* **1977,** 1033.

Consult ... *s section.*

D

CHLORHEXIDINE (Mucosal-Local)

Revision Date

Revised: 08/14/1998

Introduction

VA CLASSIFICATION (Primary/Secondary): OR500/DE101

Commonly used brand name(s): *Oro-Clense; Peridex; PerioGard.*

Note: For a listing of dosage forms and brand names by country availability, see *Dosage Forms* section(s).

Category

Antibacterial (dental)[14].

Indications

Note: Bracketed information in the *Indications* section refers to uses that are not included in U.S. product labeling.

Accepted

Gingivitis (treatment) — Chlorhexidine is indicated for use between dental visits for the treatment of gingivitis that is characterized by redness and swelling of the gingivae or gingival bleeding upon probing. [1 14 26 35]

[Gingivitis, necrotizing ulcerative, acute (treatment)] — Chlorhexidine is used along with other measures in the treatment of acute necrotizing ulcerative gingivitis (ANUG). [6 14]

[Mouth infections (prophylaxis)] or
[Mouth infections (treatment)] — Chlorhexidine is used in the treatment of mouth infections in cancer patients who are being prepared for bone marrow transplants. Chlorhexidine is also used in the management of the oral complications that occur in leukemia patients. [6 13 14 17 20 21 22]
Chlorhexidine is also used following periodontal surgery to promote healing by minimizing mouth infections and plaque that may lead to increased inflammation and infection during the healing process. [14 16 18]

[Stomatitis, denture (treatment)] — Chlorhexidine is used in the treatment of

EXHIBIT
D
ALL-STATE® INTERNATIONAL

inflammation of the oral mucosa caused by bacterial or fungal actions associated with the wearing of dentures but should not be used when inflammation is caused by poor fit or other mechanical factors associated with dentures. [4,6,14]

[Stomatitis, aphthous (treatment)] — Chlorhexidine is used in the management of minor aphthous ulcers. [14,15,16,18]

[Plaque, dental (prophylaxis)] — Chlorhexidine is used for reduction of dental plaque. [14,16,18]

Microorganisms with high susceptibility to chlorhexidine include some staphylococci, *Streptococcus mutans*, *Streptococcus salivarius*, *Candida albicans*, *Escherichia coli*, *Selenomonas*, and anaerobic propionic bacteria. *Streptococcus sanguis* has moderate susceptibility. Microorganisms with low susceptibility to chlorhexidine include *Proteus* strains, *Pseudomonas*, *Klebsiella*, and gram-negative cocci resembling *Veillonella*. [4,6]

Samples of plaque taken during a 6-month period of use with chlorhexidine oral rinse showed a 54 to 97% reduction in certain aerobic and anaerobic bacteria. However, 3 months after chlorhexidine was discontinued, the number of bacteria in the plaque had returned to baseline levels. [1,4,11,24]

A 6-month clinical study did not show any significant changes in bacterial resistance, overgrowth of potentially opportunistic organisms, or other adverse changes in the oral microbial ecosystem during the use of chlorhexidine. In addition, 3 months after chlorhexidine was discontinued, the resistance of plaque bacteria to the medication was found to be the same as before therapy was initiated. [1,4,5,24]

Pharmacology/Pharmacokinetics

Physicochemical characteristics:

Molecular weight — Chlorhexidine gluconate: 897.77 [8,10]

Mechanism of action/Effect:

Because of its positive charge, chlorhexidine gluconate is adsorbed during oral rinsing onto [33] the surfaces of teeth, plaque, and oral mucosa, which have a net negative charge. Subsequently, the adsorbed medication is gradually released from these sites by diffusion for up to 24 hours as the concentration of chlorhexidine gluconate in the saliva decreases. This release provides a continuing bacteriostatic [4,6] effect.

Chlorhexidine gluconate is adsorbed onto the cell walls of microorganisms, which causes leakage of intracellular components. At low concentrations, chlorhexidine

gluconate is bacteriostatic; at higher concentrations, chlorhexidine gluconate is bactericidal. [4 6]

Absorption:

Pharmacokinetic studies indicate that approximately 30% of chlorhexidine gluconate is retained in the oral cavity following rinsing and subsequently is slowly released into the oral fluids. [1 24]

Studies using humans and animals have shown that chlorhexidine gluconate is poorly absorbed from the gastrointestinal tract. In humans, the mean plasma level of chlorhexidine gluconate reached a peak of 0.206 mcg per gram 30 minutes following an oral dose of 300 mg. [1 4 6 24]

Elimination:

Following oral doses of 300 mg of chlorhexidine gluconate, excretion of chlorhexidine gluconate [1 33] was primarily through the feces (approximately 90%); less than 1% of chlorhexidine gluconate [1 33] was excreted in the urine. In addition, 12 hours after chlorhexidine gluconate was administered, it was not detectable in the plasma. [1 24]

Precautions to Consider

Cross-sensitivity and/or related problems

Patients sensitive to disinfectant skin cleansers containing chlorhexidine may be sensitive to chlorhexidine oral rinse also. [4]

Carcinogenicity

Carcinogenesis was not observed in a drinking water study in rats where the highest dose of chlorhexidine used was 38 mg per kg of body weight (mg/kg) per day. This dose is at least 500 times the amount that would be ingested from the recommended human daily dose of chlorhexidine oral rinse. [1 24]

Mutagenicity

Mutagenicity was not observed in 2 mammalian *in vivo* mutagenic studies with chlorhexidine. [1 24]

Pregnancy/Reproduction

Fertility —

Fertility studies have shown no evidence of impaired fertility in rats given

chlorhexidine in doses of up to 100 mg/kg per day. This dose is approximately 100 times greater than the dose a person would receive if he/she ingested 30 mL (2 capfuls) of chlorhexidine oral rinse per day. [1] [24]

Pregnancy —

Well-controlled studies in humans have not been done.

In animal studies, no evidence of harm to the fetus was observed in rats and rabbits given doses of chlorhexidine of up to 300 mg/kg per day and up to 40 mg/kg per day, respectively. These doses are approximately 300 and 40 times, respectively, greater than the dose a person would receive if she [33] ingested 30 mL (2 capfuls) of chlorhexidine oral rinse per day. [24]

FDA Pregnancy Category B. [1] [24]

Breast-feeding

Although it is not known whether chlorhexidine is distributed into breast milk, problems in humans have not been documented. In addition, studies in rats have shown no evidence of impaired parturition and no evidence of toxic effects to suckling pups when chlorhexidine was administered to dams at doses over 100 times greater than the dose a person would receive if she [33] ingested 30 mL (2 capfuls) of chlorhexidine oral rinse per day. [1] [24]

Pediatrics

Appropriate studies on the relationship of age to the effects of this medicine have not been performed in the pediatric population. Safety and efficacy have not been established. [1] [24]

Geriatrics

Appropriate studies on the relationship of age to the effects of this medicine have not been performed in the geriatric population. However, no geriatrics-specific problems have been documented to date.

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate) — not necessarily inclusive (>> = major clinical significance).

Risk-benefit should be considered when the following medical problems exist:

Anterior tooth restorations (front-tooth fillings)[30] — (anterior tooth restorations

having rough surfaces or margins may develop permanent discoloration from chlorhexidine, necessitating replacement for cosmetic reasons [1])

Periodontitis — (during clinical tests, an increase in supragingival calculus was noted in patients using chlorhexidine; it is not known whether use of chlorhexidine results in an increase in subgingival calculus [1 6 24])
(since gingival inflammation and bleeding may occur with both periodontitis and gingivitis and chlorhexidine oral rinse may reduce these signs, the presence or absence of these signs should not be used as indicators of periodontitis after the patient has been treated with chlorhexidine [1 14])

Sensitivity to chlorhexidine[24]

Patient monitoring

The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; >> = major clinical significance):

Dental examination and prophylaxis — (tartar [calculus] deposits should be removed before therapy is initiated and during therapy at intervals of 6 months or less; the patient's condition should be reevaluated at intervals of 6 months or less, including monitoring of gingival pockets, [30] because of the possible masking of coexisting periodontitis by chlorhexidine [1 14 24])

Side/Adverse Effects

Note: Chlorhexidine causes staining of oral surfaces. Staining may be visible as early as 1 week after therapy; after 6 months of use, approximately 50% of patients may have a measurable increase in tooth stain and approximately 10% may have heavy staining. Staining is more pronounced in patients who have heavier accumulations of plaque. Tooth restorations [33] having rough surfaces or margins may develop permanent staining. If this occurs on anterior surfaces, it may be necessary to replace the tooth restoration [33] for cosmetic reasons. [1 4 14 16 24]

Some patients develop an alteration in taste perception during treatment with chlorhexidine. This effect usually becomes less noticeable with continued treatment. No cases of permanent taste alteration have been reported. [1 24]

No serious systemic side/adverse effects associated with the use of chlorhexidine oral rinse were reported during the clinical trials. [1 4 27 28 29 33]

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate) — not necessarily inclusive:

Those indicating need for medical attention

Incidence rare

Allergic reaction[7,24,26] (nasal congestion; shortness of breath or troubled breathing; skin rash, hives, or itching; swelling of face)

Those indicating need for medical attention only if they continue or are bothersome

Incidence more frequent

Change in taste[1,4,5,6,24]; ***increase in tartar (calculus) on teeth***[1,4,6,24]; ***staining of teeth, mouth, tooth restorations (fillings)***[33], ***and dentures or other mouth appliances***[1,4,5,6,24]

Incidence less frequent or rare

Parotid duct obstruction[31] ***or parotitis***[31] (swollen glands on side of face or neck); ***superficial desquamative lesions***[1,4,5,6,14] (mouth irritation) — reported mainly in children ages 10 to 18 years;[1,14] the lesions are transient and may be[16] painless[14]; ***tongue tip irritation***[16]

Overdose

For more information on the management of overdose or unintentional ingestion, **contact a Poison Control Center** (see *Poison Control Center Listing*).

Treatment of overdose

Medical attention and symptomatic treatment are recommended if signs of alcohol intoxication develop or if more than 4 ounces of chlorhexidine oral rinse is ingested by a child weighing approximately 10 kg (22 pounds) [33] or less. [1,14,24,26]

Patient Consultation

As an aid to patient consultation, refer to *Advice for the Patient, Chlorhexidine (Dental)*.

In providing consultation, consider emphasizing the following selected information (>> = major clinical significance):

Before using this medication

>> Conditions affecting use, especially:

Allergy to chlorhexidine or to disinfectant skin cleansers containing chlorhexidine

Proper use of this medication

Using medication after brushing and flossing; rinsing toothpaste completely from mouth with water before using oral rinse; not eating or drinking for several hours after using oral rinse

Using the cap of the original container to measure the dose or acquiring another measuring device to use; asking your pharmacist for help

>> Swishing medication around in mouth for 30 seconds and spitting out; using full strength; not swallowing

>> Proper dosing

Missed dose: Using as soon as possible; not using if almost time for next dose; not doubling doses

>> Proper storage

Precautions while using this medication

Not rinsing mouth with water immediately after using medication, since doing so will increase medication's bitter aftertaste and may decrease medication's effect [33]

Medication causes change in taste; change may last up to 4 hours after dose; change in taste should be less noticeable as medication is continued; after medication is discontinued, taste should return to normal

Staining and increase in tartar (calculus) may occur; brushing with tartar-control toothpaste and flossing teeth daily to help reduce tartar build-up; visiting dentist at least every 6 months for teeth cleaning and gum examination

>> Getting emergency help at once if a child weighing 22 pounds (10 kg) or less drinks more than 4 ounces of dental rinse or if any child experiences symptoms of alcohol intoxication, such as slurred speech, sleepiness, or staggering or stumbling walk, after drinking the dental rinse

Side/adverse effects

Signs of potential side effects, especially allergic reaction

Dental Dosage Forms

Note: Bracketed uses in the *Dosage Forms* section refer to categories of use and/or indications that are not included in U.S. product labeling.

CHLORHEXIDINE GLUCONATE ORAL RINSE

Usual adult dose

Gingivitis —

Topical, to the gingival membranes, 15 mL of a 0.12% oral rinse for 30 seconds two times a day after brushing and flossing teeth. [1] [24] [26] [35]

Note: Therapy with chlorhexidine oral rinse should start immediately following a dental prophylaxis. [1] [24] [26]

[Denture stomatitis] —

Soak the dentures in chlorhexidine oral rinse 0.12% for 1 to 2 minutes two times a day. Rinsing the mouth for 30 seconds two times a day or brushing the gums or dentures two times a day with chlorhexidine oral rinse 0.12% may also be required. [4] [14]

Usual pediatric dose

Children up to 18 years of age — Safety and efficacy have not been established. [24]

Strength(s) usually available

U.S. —

0.12% (Rx) [*Peridex*[1,23,26] (alcohol 11.6%); *PerioGard*[23,35] (alcohol 11.6%)] [GENERIC][38]

Canada —

0.12% (Rx) [*Oro-Clense*[36] (alcohol); *Peridex*[37] (alcohol)].

Packaging and storage:

Store above freezing at a temperature not exceeding 25 °C (77 °F), unless otherwise specified by manufacturer. Protect from light. [1] [10] [24] [26]

Preparation of dosage form:

If the medication is not commercially available, it may be compounded as follows — 3 mL chlorhexidine gluconate 20% should be added to approximately 200 mL

distilled water. Separately, 5 mL essence of peppermint should be combined with 5 mL ethanol 95% and then 15 mL glycerin should be added. This mixture should be combined with the chlorhexidine and water solution and enough distilled water added to make 500 mL. [32]

Auxiliary labeling:

- Do not swallow. [26]
- Do not dilute. [26]

Note:

Dispense with patient package insert. [1] [2]

Dispense in original container, which includes a measuring cap, or in an amber glass container and include a device for measuring 15 mL (1/2 fluid ounce). [3]

References

[1] Peridex package insert (Procter & Gamble — US), Rev 8/86, Rec 1/88.

[2] Peridex patient package insert (Procter & Gamble — US), Rec 1/88.

[3] Peridex product label (Procter & Gamble — US), Rec 1/87.

[4] Chlorhexidine. Biological Therapies in Dentistry 1986 Oct; 2(5).

[5] Chlorhexidine and plaque control. Dent Manage 1986 May: 58-60.

[6] A review of the literature on use of chlorhexidine in dentistry. J Am Dent Assoc 1986 Jun: 863-9.

[7] Moghadam BKH, Drisko CL, Gier RE. Chlorhexidine mouthwash-induced fixed drug eruption. Oral Surg Oral Med Oral Path 1991 Apr; 71: 431-4.

[8] Fleeger CA, editor. USAN 1993. USAN and the USP dictionary of drug names. Rockville, MD: The United States Pharmacopeial Convention, Inc., 1992.

[9] Open.

[10] Reynolds JEF, editor. Martindale's The extra pharmacopeia. 28th ed. London: The Pharmaceutical Press, 1982: 554.

[11] P&G finds rinse with chlorhexidine effective in tests. Drug Topics 1986 Jun 2:

72.

[12] Open.

[13] Instant Up-Date, 1987 Feb: 2.

[14] Panel comments, 5/87.

[15] Hunter L, Addy M. Chlorhexidine gluconate mouthwash in the management of minor aphthous ulceration. Br Dent J 1987 Feb 7; 162: 106-10.

[16] Panel comments, 7/87.

[17] Ferretti, Ash, Brown, et al. Chlorhexidine for prophylaxis against oral infections and associated complications in patients receiving bone marrow transplants. J Am Dent Assoc 1987 Apr; 114: 461-7.

[18] Panel comment, 7/87.

[19] Open.

[20] Reviewer comment, 2/88.

[21] Ferretti, et al. Chlorhexidine for prophylaxis against oral infections and associated complications in patients receiving bone marrow transplants. J Am Dent Assoc, 1987 Apr; 114: 461-7.

[22] Spiers, et al. Infection prevention in patients with cancer: microbiological evaluation of portable laminar air flow isolation, topical chlorhexidine, and oral non-absorbable antibiotics. J Hyg 1980; 84: 457-65.

[23] Reviewers' responses to Disulfiram monograph revision of 8/87 referring to interaction with chlorhexidine.

[24] Peridex (Procter & Gamble). In: PDR Physicians' desk reference. 45th ed. 1991. Montvale, NJ: Medical Economics Data, 1991: 1742.

[25] Open.

[26] Peridex (Procter & Gamble). In: PDR Physicians' desk reference. 47th ed. 1993. Montvale, NJ: Medical Economics Data, 1993: 1867-8.

[27] Okano M, et al. Anaphylactic symptoms due to chlorhexidine gluconate. Arch Dermatitis 1989 Jan; 125: 50-2.

[28] Bergqvist-Karlsson A. Delayed and immediate-type hypersensitivity to chlorhexidine. Contact Dermatitis 1988 Feb; 18: 84-8.

[29] Fisher AA. Contact urticaria from chlorhexidine. Cutis 1989 Jan; 43: 17-8.

[30] Panel comment, 3/92.

[31] Panel comment, 3/92.

[32] Chlorhexidine mouthwash. New Drugs/Drug News 1991 Jul/Aug.

[33] Panel comments, 11/93.

[34] Open.

[35] PerioGard package insert (Colgate — US), Rev 11/93, Rec 4/94.

[36] Oro-Clense (Germiphene). In: Krogh CME, editor. CPS Compendium of pharmaceuticals and specialties. 33rd ed. Ottawa: Canadian Pharmaceutical Association; 1998. p. 1233.

[37] Peridex (Proctor & Gamble). In: Krogh CME, editor. CPS Compendium of pharmaceuticals and specialties. 33rd ed. Ottawa: Canadian Pharmaceutical Association; 1998. p. 1298.

[38] Chlorhexidine gluconate (Teva). In: PDR Physicians' desk reference. 52nd ed. 1998. Montvale, NJ: Medical Economics Data; 1998. p. 2923.

- **Database Title:**
  - STAT!Ref Online Electronic Medical Library
- **Editor:**
  - Thomson Healthcare, Inc.
- **ISBN:**
  - 1-56363-514-3

- **ISSN:**
  - 0740-4174
- **Publication City:**
  - Greenwood Village, CO
- **Publication Year:**
  - 2005
- **Publisher:**
  - Thomson MICROMEDEX
- **Date Accessed:**
  - 7/7/2005 10:29:09 AM PST (GMT -08:00)
- **Electronic Address:**
  - http://online.statref.com/document.aspx?fxid=6&docid=3511
- **Location In Book:**
  - USP DI® DRUG INFORMATION FOR THE HEALTH CARE PROFESSIONAL - 25th Ed. (2005)
    "C" MONOGRAPHS
    CHLORHEXIDINE (Mucosal-Local)
- **Date Posted:**
  - 5/17/2005 4:49:26 PM PST (GMT -08:00)
- **Book Title:**
  - USP DI® Drug Info. for the Health Care Pro. - 25th Ed. (2005)

E

Entrez PubMed
Overview
Help | FAQ
Tutorial
New/Noteworthy
E-Utilities

PubMed Services
Journals Database
MeSH Database
Single Citation Matcher
Batch Citation Matcher
Clinical Queries
Special Queries
LinkOut
My NCBI (Cubby)

Related Resources
Order Documents
NLM Catalog
NLM Gateway
TOXNET
Consumer Health
Clinical Alerts
ClinicalTrials.gov
PubMed Central

1: J Dent Res. 1989 Jun;68(6):1132-4. Related Articles, Links

In vivo effects of zinc and chlorhexidine on dental plaque ureolysis and glycolysis.

Giertsen E, Scheie AA, Rolla G.

Department of Pedodontics and Caries Prophylaxis, Faculty of Dentistry, University of Oslo, Norway.

We assessed the in vivo effects of zinc and chlorhexidine (CH) on plaque ureolysis and glycolysis in five volunteers. We monitored plaque pH by a surface glass electrode on two teeth in each subject, after topical application of either 5% wt/vol urea or 5% wt/vol glucose solutions. The recordings were repeated 15 and 75 min after a single mouthrinse, with either 20 mmol/L zinc acetate or 0.33 mmol/L CH diacetate. Ureolytic activity decreased significantly (p less than 0.03) up to 75 min after a single mouthrinse with the zinc-containing test solution. CH had no effect on plaque ureolytic activity. Acid production by dental plaque decreased significantly (p less than 0.01) up to 75 min after a single mouthrinse with either the zinc- or the CH-containing test solution.

PMID: 2808872 [PubMed - indexed for MEDLINE]

EXHIBIT
E
ALL-STATE® INTERNATIONAL

About Entrez

Text Version

Entrez PubMed
Overview
Help | FAQ
Tutorial
New/Noteworthy
E-Utilities

PubMed Services
Journals Database
MeSH Database
Single Citation Matcher
Batch Citation Matcher
Clinical Queries
Special Queries
LinkOut
My NCBI (Cubby)

Related Resources
Order Documents
NLM Catalog
NLM Gateway
TOXNET
Consumer Health
Clinical Alerts
ClinicalTrials.gov
PubMed Central

All: 2 Review: 0

Items 1 - 2 of 2 One page.

☐ **1:** Oral Microbiol Immunol. 1995 Dec;10(6):360-4. Related Articles, Links

Mechanism of inhibition of glycolysis in Streptococcus mutans NCIB 11723 by chlorhexidine.

Iwami Y, Schachtele CF, Yamada T.

Department of Oral Biochemistry, Tohoku University School of Dentistry, Sendai, Japan.

Inhibition of the rate of acid production from glucose by the cells of Streptococcus mutans NCIB 11723 was directly related to the concentrations of 0.075 to 0.20 mM chlorhexidine. Lactate production was inhibited to a greater extent than acetate and formate. Quantification of glycolytic intermediates revealed that the steps in glycolysis inhibited by chlorhexidine were the reactions catalyzed by phosphofructokinase and glyceraldehyde 3-phosphate dehydrogenase and/or phosphoglycerate kinase. However, the activities of these enzymes were not decreased in cells treated with the inhibitor. It was demonstrated that chlorhexidine caused leakage of metabolites from the cells. Our results indicate that the decreased rate of glycolysis caused by chlorhexidine is due to the leakage of metabolic intermediates and not to direct effects on enzymes involved in glycolysis by S. mutans NCIB 11723.

PMID: 8602344 [PubMed - indexed for MEDLINE]

☐ **2:** Oral Microbiol Immunol. 1995 Dec;10(6):360-4. Related Articles, Links

Mechanism of inhibition of glycolysis in Streptococcus mutans NCIB 11723 by chlorhexidine.

Iwami Y, Schachtele CF, Yamada T.

Department of Oral Biochemistry, Tohoku University School of Dentistry, Sendai, Japan.

EXHIBIT F ALL-STATE® INTERNATIONAL

Entrez PubMed
Overview
Help | FAQ
Tutorial
New/Noteworthy
E-Utilities

PubMed Services
Journals Database
MeSH Database
Single Citation Matcher
Batch Citation Matcher
Clinical Queries
Special Queries
LinkOut
My NCBI (Cubby)

Related Resources
Order Documents
NLM Catalog
NLM Gateway
TOXNET
Consumer Health
Clinical Alerts
ClinicalTrials.gov
PubMed Central

1: Arch Oral Biol. 1984;29(11):871-8. Related Articles, Links

Evidence that glucose and sucrose uptake in oral streptococcal bacteria involves independent phosphotransferase and proton-motive force-mediated mechanisms.

Keevil CW, Williamson MI, Marsh PD, Ellwood DC.

Sugar transport and glycolysis in Streptococcus sanguis NCTC 7865, Streptococcus mitis ATCC 903, Streptococcus salivarius NCTC 8606 and several strains of Streptococcus mutans were investigated by following the rate of acid production by washed bacteria at a constant pH of 7.0. The phosphoenolpyruvate-phosphotransferase system (PTS) was inhibited by low concentrations of chlorhexidine. When this PTS-inhibitory concentration of chlorhexidine was added to cells washed and re-suspended in KCl, glucose uptake and glycolysis continued at a greatly-reduced rate. Chlorhexidine abolished glucose and sucrose uptake and metabolism in bacteria washed and incubated in saline. The Na+-inhibition was reproduced in KCl-washed bacteria using the cyclic peptide ionophores, valinomycin and gramicidin, to dissipate K+ and H+ gradients across the cell membrane. Glucose metabolism by Strep. mutans B13 was more resistant to chlorhexidine than that of Strep. mutans NCTC 10449 or Strep. sanguis but was more sensitive to the ionophores. Valinomycin had a greater inhibitory effect on strain B13 than the other two. That ion gradients are important in the chlorhexidine-resistant glucose-uptake mechanism was confirmed using the classical uncoupling agents, carbonylcyanide-m-chlorophenylhydrazone, 2,4-dinitrophenol and KSCN. Glucose metabolism was inhibited in the presence of both the uncouplers and the PTS-inhibitory concentration of chlorhexidine and significant inhibition was also observed in the absence of the PTS inhibitor. Lactate or the ATPase inhibitor, dicyclohexyl carbodiimide (DCCD), had similar inhibitory effects on the non-PTS uptake system.(ABSTRACT TRUNCATED AT 250 WORDS)

PMID: 6097204 [PubMed - indexed for MEDLINE]

EXHIBIT
G
ALL-STATE® INTERNATIONAL

Entrez PubMed
Overview
Help | FAQ
Tutorial
New/Noteworthy
E-Utilities

PubMed Services
Journals Database
MeSH Database
Single Citation Matcher
Batch Citation Matcher
Clinical Queries
Special Queries
LinkOut
My NCBI (Cubby)

Related Resources
Order Documents
NLM Catalog
NLM Gateway
TOXNET
Consumer Health
Clinical Alerts
ClinicalTrials.gov
PubMed Central

1: Caries Res. 1993;27(4):298-302. Related Articles, Links

The effect of chlorhexidine and zinc/triclosan mouthrinses on the production of acids in dental plaque.

van der Hoeven JS, Cummins D, Schaeken MJ, van der Ouderaa FJ.

Laboratory of Oral Microbiology, Research Program TRIKON, University of Nijmegen, The Netherlands.

Chlorhexidine, and zinc in combination with triclosan, are used as anti-plaque agents in the prevention of gingivitis. The multifunctional activity of these compounds against bacterial cells has been proposed to include interference with sugar transport and reduction of glycolysis. In this study the ability of the agents to reduce acid production in dental plaque in vivo has been investigated. Samples of smooth-surface plaque were collected from individuals who had been rinsing for several weeks with (a) chlorhexidine (0.12%, Peridex); a combination of zinc and triclosan in mouthwashes containing (b) high and (c) low concentrations of humectant; or (d) a control mouthwash. Analyses using isotachophoresis showed that resting plaques in the chlorhexidine and zinc/triclosan groups contained less acetate than the control group. Acids were also measured 15 min after a glucose rinse. Compared with the control, the amount of lactate was significantly decreased (45%) in the chlorhexidine group, while lactate reduction (20%) in the zinc/triclosan (high humectant) group was not statistically significant.

Publication Types:
- Clinical Trial
- Controlled Clinical Trial

PMID: 8402805 [PubMed - indexed for MEDLINE]

EXHIBIT H ALL-STATE® INTERNATIONAL

Entrez PubMed
Overview
Help | FAQ
Tutorial
New/Noteworthy
E-Utilities

PubMed Services
Journals Database
MeSH Database
Single Citation Matcher
Batch Citation Matcher
Clinical Queries
Special Queries
LinkCut
My NCBI (Cubby)

Related Resources
Order Documents
NLM Catalog
NLM Gateway
TOXNET
Consumer Health
Clinical Alerts
ClinicalTrials.gov
PubMed Central

1: Caries Res. 1995;29(3):181-7. Related Articles, Links

Effects of chlorhexidine-fluoride mouthrinses on viability, acidogenic potential, and glycolytic profile of established dental plaque.

Giertsen E, Scheie AA.

Department of Oral Biology, Faculty of Dentistry, University of Oslo, Norway.

Inhibition of dental plaque acidogenicity by chlorhexidine (CHX) mouthrinses has been ascribed to a long-lasting bacteriostatic effect due to binding of CHX to oral surface structures combined with a slow release rate from the binding sites. The present aims were to study the effects of CHX-containing mouthrinses on the viability and glycolytic activity of established plaque in order to assess the bactericidal versus the bacteriostatic effects. Following 2 days of plaque accumulation, three groups of 10 students rinsed with either 12.0 mM NaF, 0.55 mM CHX plus NaF, or with 2.2 mM CHX plus NaF. Plaque samples were collected before and 90 min after mouthrinsing. The pH in pooled pre- and post-rinse plaque samples was recorded before and up to 10 min after the addition of D-[U-14C]glucose. Total colony-forming units in each sample were determined. High-performance liquid chromatography analyses showed lactate to be the major extracellular glycolytic metabolite in all samples. CHX-NaF markedly reduced the colony-forming units, the pH fall from fermentation of glucose, as well as glucose consumption and lactate formation, whereas NaF alone exhibited no such effects. The reduction of glucose consumption by the CHX-NaF mouthrinses corresponded to the reduction of colony-forming units, indicating no bacteriostatic effect. The plaque pH in vivo was monitored in each student 90 min after mouthrinsing with the test solutions prior to and up to 1 h after a sucrose mouthrinse using touch microelectrodes. The CHX-NaF mouthrinses reduced the fall in pH significantly ($p < 0.05$) as compared with the NaF mouthrinse.(ABSTRACT TRUNCATED AT 250 WORDS)

Publication Types:
- Clinical Trial